Citation:

Whitten CF, Stewart RA. The effect of dietary sodium in infancy on blood pressure and related factors. *Acta Pediatr Scand.* 1980; 279: 2-17.

PubMed ID: 7001854

Study Design:

Prospective cohort

Class:

C - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

- To determine the effects in infants of a low vs. high level of salt intake on blood pressure (BP) and several related metabolic parameters
- To determine whether or not over a period of years, there was a difference in the salt intake and BP of the two groups of participants.

Inclusion Criteria:

None identified.

Exclusion Criteria:

None reported.

Description of Study Protocol:

Recruitment

- Participants were recruited from well baby clinics and the parents agreed to restrict the feeding of their infants during the test period to the foods provided
- The mothers were paid to maintain records of the quantity of foods eaten.

Design

- One group received foods that were intended to yield a sodium intake of 2mEq Na per 100kcal (low sodium) and the other 9mEq Na per 100 kcal (high sodium)
- Subjects were provided with food and followed prospectively.

Intervention

- *All groups:*
  - The infants were provided food and formula which differed primarily in its sodium content
  - The infants were fed at home for a five-month period beginning at three months of age and ending at eight months of age
  - A variety of 14 infant foods, including special infant formula, was delivered to the infant's home on a biweekly basis
  - The solid foods were prepared from single batch lots at a commercial baby food plant
  - No dietary restrictions of monitoring were instituted from eight months to eight years of age. The

subjects were free to follow the dietary customs prevailing in their homes
- *Low-sodium group:*
  - Foods were intended to yield a sodium intake of 2mEq Na per 100kcal
  - Solid foods contained no added salt in the vegetable, cereal, and meat items
  - The low-sodium formula was prepared by diluting regular Modilac with Modilac formula treated by reverse osmosis to remove the sodium
- *High-sodium group:*
  - Foods were intended to yield a sodium intake of 9mEq Na per 100kcal
  - Solid foods contained the level of salt used in late 1969, that is, approximately 0.75% added salt in the vegetable, cereal and meat items.
  - The high-sodium formula was prepared by adding sodium chloride to regular Modilac.

Statistical Analysis

Statistical analyses were made using Student's T-test and P values less than 0.05 were considered to be significant. Means, standard deviations (SD), coefficients of variation (CV) correlation coefficients (R) for various data sets were calculated by standard procedures.

Data Collection Summary:

Timing of Measurements

- At four, six and eight months of age, the infants were admitted to the Clinical Research Center of the Children's Hospital of Michigan for three days to obtain measurements of BP, height, weight and skinfold thickness, extracellular fluid volume, plasma rennin, serum sodium and potassium, urinary excretion of sodium, potassium, aldosterone and 17 ketogenic steroids. The infants were fed from the same batch of foods used for home delivery and were placed on metabolic frames to facilitate collection of urine
- At approximately one year of age, measurements were made of height and weight
- During their eighth year, a follow-up study was conducted to measure BP, urinary sodium excretion and salt usage.

Dependent Variables

Salt use at 8 years:

- The mother of each child (with one exception, the father) was interviewed by the principal investigator
- The mothers were asked to describe their son's use of salt. The responses were categorized into three groups:
  - The child never adds salt
  - The child sometimes adds salt or salts some items
  - The child usually adds salt or salts everything
- The mothers were also asked to comment on their use of salt during the preparation of food, falling into one of three categories:
  - "Not very much"
  - "Average"
  - "A lot"
- For the four, six and eight months' assessments, the BP measurements were made by auscultation using an Air Shield Blood Pressure Monitor attached to the right arm of infant which automatically inflated the cuff to 180mmHg every five minutes
- Readings were recorded six to 12 times during the three daily nursing shifts over a 72-hour period or longer
- Only determinations made while the infants were asleep and approximately an hour after feeding were used in the compilation of results
- The BP of the eight-year old boys was measured with a mercury Baunometer while sitting, sitting after resting 10 minutes and supine. Three measurements in each position were taken on each of the three consecutive days
- The infants were weighed on a calibrated metabolic infant scale
- Heights were measured with a specially constructed infant measuring board
- Biceps skinfold thickness was measured with a Herpeden skinfold caliper
- At eight years, the weight was measured with a standard scale
- Height was measured with a calibrated Herpeden Stadiometer
- The heights and weights were compared with normal standards using the National Center Health Statistics tables

- Sodium and potassium analyses were made with Instrumentation Laboratory flame photometer
- Foods were prepared for analysis by extraction with nitric acid, serum levels were made by direct reading and urine concentrations were determined after dilution
- Urinary aldosterone was determined by a modification of the double-isotope procedure of Laragh et al and 17-ketogenic steroids by the Sobel technique
- Plasma rennin was determined by the NEN Biomedical Laboratory using the method of Gunnels et al
- Extracellular fluid volume (ECF) was calculated by the bromide space technique using a procedure described by Owen et al. A 2% sodium bromide solution was injected subcutaneously at the level of 3ml per kg of body weight. Serum and urinary bromide was estimated prior to injection and following a three-hour period. Urine collection started with the last voiding before injection of bromide and ended with a voiding not earlier than one-half hour before the end of the three-hour period. The ECF, expressed as the percent of body weight made up from interstitial fluid and plasma volume and exchangeable chloride, was calculated from bromide space
- Hemoglobin, blood urea nitrogen (BUN), serum chloride, cholesterol, creatinine and hydroxyproline and total plasma protein was determined by standard laboratory procedures used in the hospital laboratory
- Infant dietary intake of sodium was assessed from mothers' records of foods consumed by the infant.

Description of Actual Data Sample:

- *Initial N:* 27 infants (13 low salt, 14 high salt)
- *Attrition (final N):* 23 boys (11 low salt, 12 high salt) were available for follow-up at eight years
- *Age:* All infants, initiating intervention at three months until eight months, and then followed up at eight years
- *Health:* Products of full-term pregnancies; had experienced no illnesses other than respiratory infections
- *Ethnicity:* All black males
- *Anthropometrics:*
  - The infants were well within the normal body weight range at birth and throughout the test period. The difference in weight gain during this period was significantly higher for the low-salt group (P=0.02) even though there was no significant (NS) difference in caloric intake
  - There was NS difference between the biceps skinfold thickness at four months, whereas the infants on a low-salt diet had a significantly higher skinfold thickness at eight months (P=0.05)
  - At one year of age, both groups were slightly below the 50th percentile for weight but there was NS difference between the two groups with respect to weight gain, skinfold thickness, arm circumference or the Quetelet Index
  - At eight years, the higher mean body weight of the low salt group was due primarily to the excessive weight gain of one subject, and the difference between the two groups was not statistically significant
  - Likewise, there was NS difference between the two groups with respect to skinfold thickness, arm circumference or the Quetelet Index at eight years
- *Location:* Michigan, US.

Summary of Results:

Key Findings

The average (SD) for sodium intake was found to be 1.93±0.10mEq Na per 100kcal and 9.25±0.50mEq Na per 100kcal for the low- and high-salt groups respectively. These intakes represented the sixth and 99th percentiles of sodium intake of the US sample of 364 infants surveyed in 1969 and the 21st and 99.5th percentiles of a US sample of 151 infants surveyed in 1977.

The Effect of Dietary Sodium in Infancy on Blood Pressure					
	Four Months Mean±SD	**Eight Months Mean±SD**	**Eight Years, Sitting Mean±SD**	**Eight Years, 10 Minutes Rest Mean±SD**	**Eight Years, Supine Mean±SD**
Diastolic BP (mmHg)					
Low salt	49±5	48±5	74±5	74±5	75±5

High salt	50±5	49±5	77±5	76±6	76±5
P-value	0.6	0.5	0.1	0.4	0.6
Systolic BP (mmHg)					
Low salt	97±21	88±5	103±7	101±6	103±5
High salt	102±16	90±6	105±7	102±5	103±6
P-value	0.5	0.4	0.5	0.6	1.0

- At four and eight months, there was wide variation in both the systolic BP (SBP) and diastolic BP (DBP) measurements. This variability appears to be unrelated to the time of date or to the pediatric nurse taking the readings
- There was NS difference in either the mean SBP or DBP of the two groups at either four or eight months of age (P=0.4)
- The coefficient of variation ranged from 11% to 20% for both the SBP and DBP at four months of age. By eight months of age, the coefficient of variation dropped to 6% to 10%
- The overall mean SBP and DBP for the low- and high-salt groups were practically identical at eight years
- The differences between the two groups with respect to overall measurements as well as the measurements obtained in the three positions were NS (P=0.4 to 1.0)
- Both SBP and DBP was significantly correlated with weight, weight gain from infancy, Quetelet Index and skinfold thickness, but not with urine volume, sodium excretion, perceived salt usage or BUN
- Diastolic BP at eight months and eight years were significantly correlated (R=0.65, P=0.01), but SBPs were NS correlated.

The Effect of Feeding Salted and Unsalted Foods to Infants for One, Three and Five Months on Various Body, Blood and Urine Factors

Feeding Period	One Month			Three Months			Five Months		
Diet	**Unsalted Mean±SD**	**P-value**	**Salted Mean±SD**	**Unsalted Mean±SD**	**P-value**	**Salted Mean±SD**	**Unsalted Mean±SD**	**P-value**	**Salted Mean±SD**
Daily Intake									
Kcal	560±186	0.80	642±103	716±155	0.90	715±163	768±153	0.90	785±199
mEq Na	12.8±3.7	0.001	46.1±87	14.2±3.2	0.001	70.3±15.2	15.2±15.2	0.001	81.1±18.8
Blood Composition									
Serum Na, mEq	137.3±1.4	0.05	135.7±2.06	136.7±1.8	1.00	136.6±1.90	137.2±1.7	0.70	137±2.25
Serum K, mEq	5.23±0.20	0.70	5.28±0.29	5.10±0.33	0.70	5.04±0.30	5.10±0.3	0.60	5.07±0.25
Basal Metabolic Rate							51.4±3.1	0.80	52.0±5.8
Urinary Excretion									
Urine volume, ml per 72 hours	1,101±228	0.50	1,212±408				1,124±310	0.90	1,106±395

Sodium, mEq per 24 hours	7.6±2.2	0.001	51.6±11.0				11.3±3.2	0.001	54.8±9.4
Potassium, mEq per 24 hours	11.6±2.6	0.001	18.1±3.4				13.1±2.1	0.001	17.2±2.8

- ECF volumes at four and eight months of age were within the normal range for infants. There was no statistically significant difference between the high-salt and low-salt group at four months. ECF volumes at four and eight months of age were within the normal range for infants. There was no statistically significant difference between the high-salt and low-salt group at four months
- The difference in ECF and exchangeable Cl at eight months was statistically significant (P=0.02)
- Seven out of nine infants on the low-salt diet showed a decrease in ECF, while seven of nine infants on the high-salt diet showed an increase
- The mean three-day urine volumes for the two groups were NS different at four or eight months (P=0.50 and 0.90 respectively)
- Urine volume at eight months of age was independent of ECF volume. The correlation coefficients were -0.035 and -0.249, showing NS relationship between ECF and urine volume
- The infants on the high-salt diet at eight months of age excreted 4.8 times as much sodium as the infants on the low-salt diet, a difference that was highly significant (P=0.001)
- Higher levels of plasma rennin and urinary aldosterone excretion were found with the low-sodium diet than with the high sodium diet (P=0.001)
- The serum sodium was higher in the low-salt group than the high-salt group at four months. However, there was NS difference at six and eight months.
- At four and eight months, there was little or no correlation of either SBP or DBP with either Na or Na/K excretion.
- The mean values for serum creatinine, chloride and cholesterol, plasma total proteins and albumin and BUN at four, six and eight months were within the normal range and there was NS difference between the two groups except that the total serum protein was significantly higher in the high-salt group at eight months (P=0.05).

Salt Use Preference			
	Child's Salt Use Mean±SD	**Mother's Salt Use Mean±SD**	**Total Salt Use (sum of child and mother's) Mean±SD**
High-salt group	1.42±0.67	1.50±0.67	2.02±1.00
Low-salt group	2.09±0.83	1.54±0.93	3.64±1.50
P-value	0.12	0.08	0.09
Legend: Responses from one to three.			

- Differences in average salt usage scores and the average sodium excretions for the two groups were NS
- Correlations between sodium excretion and salt usage scores were NS except for sodium excretion and child's salt use in the high-salt group, suggesting that mothers of children in the high-salt group accurately judged their child's salt usage.

Author Conclusion:

- A formula-baby food diet providing 9.25±0.50mEq Na per 100kcal (99th percentile) did not affect the BP of black male infants during the five-month feeding period from three to eight to eight months of age. Nor did this diet influence BP or preference for salt in later childhood (eight years).
- An identical no-salt diet providing 1.93±0.10mEq Na per 100kcal (6th percentile) supplied ample sodium for growth, obligatory sodium losses and maintenance of normal serum sodium and chloride levels

- A statistically significant expansion of ECF (6%) with the high-salt diet did not result in correlated increases of body weight, blood pressure, urine volume or sodium excretion
- At eight years of age, BP was correlated with BP at eight months of age, and also with weight, skinfold thickness and Quetelet index, but not with salt intake as indicated by Na excretion or the mothers' perception of salt preference and usage.
- Interviews with the mothers indicated that an imprint in infancy would have to persist through a period of several years when the salt intake is not based upon the child's likes or dislikes but is determined solely by the food preparer. If imprinting occurs, it is more likely that several years of conditioning occurring between early infancy and the time when the child can verbally express salt preference or handle the salt shaker may determine the individual salt preferences.
- There is no apparent explanation for the slightly larger ECF in the infants on the high-salt diet. It could be the result of a larger retention of sodium, but the larger ECF is not reflected in the weight gain of infants, for infants on the high-salt diets gained weight at a slower rate than those on the low-salt diet.

Reviewer Comments:

- *Selection of subjects was not adequately described. Although the authors stated that all infants were black males, it is difficult to determine if this was their target population or if the were unable to recruit other ethnicities or females*
- *Allocation of subjects to groups was not described. There is insufficient information to determine whether the subjects were randomly assigned, non-randomly assigned or parental preference was involved. This information would be necessary to determine what types of bias to consider when interpreting results*
- *Baseline characteristics of patients other than anthropometrics were not given. Information that may have been useful includes educational status of the parents, socioeconomic status, family history of hypertension and other risk factors for elevated blood pressure. Because this information was not given, it is difficult to determine whether or not any differences should have been adjusted in statistical analyses*
- *Reasons for loss to follow-up at eight years were not given*
- *Blinding status of the subjects' families and investigators was not reported. It is unknown if the study design was single or double blinded or if it was open-label*
- *It is uncertain whether or not data collectors were blinded to treatment groups. Although most of the endpoints are lab data, BP readings are less objective measures when read by auscultation of nurses, as they were in this study*
- *Clinical significance was not addressed because results were not statistically significant.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes

1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	No
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	No
2.2.	Were criteria applied equally to all study groups?	???
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	No
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	No
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	No
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	???
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	???
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	???
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	???
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A

5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	No
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	???
8.6.	Was clinical significance as well as statistical significance reported?	N/A
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes

9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	No
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	???